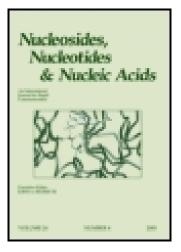
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Synthesis of [1-[2',5'-bis-O-(t-Butyldimethylsilyl)-β- L-ribofuranosyl] thymine]-3'-spiro-5"-(4"-amino-1",2"oxathiole-2",2"-dioxide) (L-TSAO-T)

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SYNTHESIS OF [1-[2',5'-BIS-O-(t-BUTYLDIMETHYLSILYL)-β-L-RIBOFURANOSYL]THYMINE]-3'-SPIRO-5"-(4"-AMINO-1",2"-OXATHIOLE-2",2"-DIOXIDE) (L-TSAO-T)

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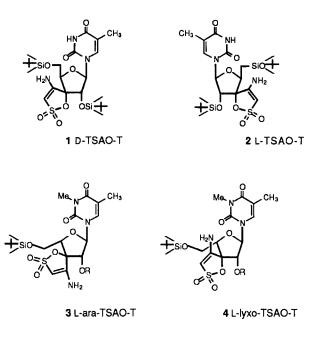
Abstract: Derivatives of TSAO-T based upon pentofuranose sugars with the L-configuration have been prepared and evaluated as inhibitors of HIV-1 induced cytopathicity.

INTRODUCTION

Since the discovery that the TSAO family of compounds, the prototype of which is $[1-[2',5'-Bis-O-(t-butyldimethylsilyl)-\beta-D-ribo-furanosyl]thymine]-3'-spiro-5"-(4"-amino-1", 2"-oxathiole-2",2"-dioxide) designated here as D-TSAO-T 1,¹ are highly potent, specific HIV-1 reverse transcriptase inhibitors; many modifications of the basic structure have been studied.²⁻⁵$

Some 2',3'-dideoxy-L-pyrimidine nucleosides such as β -L-ddC and (-)-2',3'dideoxy-3'-thiacytidine [(-)-3TC] exhibit strong anti-HIV activity in cell culture and are targeted at the retroviral reverse transcriptase.^{6,7} With this in mind and to compare its activity with D-TSAO-T **1**, the synthesis of the L-isomer of TSAO-T, henceforth known as L-TSAO-T **2**, was carried out.

Furthermore, studies on the effects of changing the nature of the protecting groups at the 2'-O and 5'-O positions on the antiviral activity ⁵ have shown the relative importance of the 5'-O-t-BDMS substituent. It was of particular interest to see if the position of this group was vital to the inhibitory function of TSAO-T. Since it was not known if a change in the configuration at the C-4 position would affect the accessability of the amino group at C-4" of the spiro moiety it was of importance to synthesise both the L-arabino 3 and L- *lyxo* **4** isomers of TSAO-T. Thus, a synthetic route starting with L-*arabino*-thymine **8** was devised.



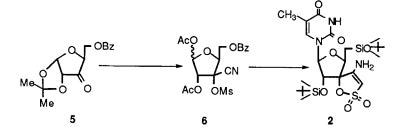
SYNTHESIS

(a) The synthesis of L-TSAO-T 2

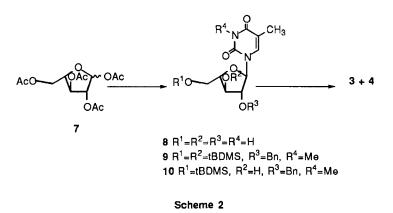
Following the procedure for the synthesis of 1^1 the L-analogue 2 was synthesised from L-xylose via the key intermediates 5 and 6 (Scheme 1).

(b) The synthesis of L-arabino-TSAO-T 3 and L-lyxo-TSAO-T 4

Beginning with L-arabino-furanose-1,2,3,5-tetraacetate 7^8 (Scheme 2), glycosylation with persilylated thymine followed by deprotection yielded the nucleoside







8. Silylation with *tert*-BDMSCl in pyridine gave a mixture of products, of which only one disubstituted isomer **9** was isolated (50% yield).

N-Methylation yielded 9 and 2'-*O*-benzylation gave 10. The 3'-*O*-silyl group was removed selectively with tetrabutylammonium fluoride in dry acetone⁹ to give 11. Oxidation of 11 followed by cyanomesylate formation gave a mixture of the isomers which were ring closed with Cs₂CO₃ in CH₃CN to give the compounds 3 and 4.

The compounds 1 to 4 have been tested for anti-HIV-1 inhibition in CEM and MT-4 cell lines, but none of the modified compounds (2 to 4) have shown significant activity at subtoxic concentrations.

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